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## EUROPEAN PATENT APPLICATION

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㉙ **Ophthalmic preparations containing sarpogrelate for reducing intraocular pressure**

㉚ An ophthalmic preparation for reducing intraocular pressure comprises 2-[3-dimethylamino-2-(2-carboxyethoxy)-propionyloxy]-2'-methoxybibenzyl or a salt thereof.

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This invention relates to ophthalmic preparations comprising 2-[3-dimethylamino-2-(2-carboxyethoxy)propionyloxy]-2'-methoxybibenzyl or a salt thereof which exhibit excellent intraocular pressure reducing activity.

Glaucoma, being heretofore considered an important problem in the field of ophthalmology, refers to the symptoms characterized by elevation of intraocular pressure over the normal range of 10 to 20 mmHg and manifestation of impaired visual function and is regarded as one of intractable ophthalmologic diseases. Currently, glaucoma is treated with the aim to control intraocular pressure. Referring to the pharmacotherapy of glaucoma, cholinergic drugs being represented by pilocarpine and anticholinesterase agents have long been employed as an ophthalmic preparation. However, these drugs exhibit strong side effects, such as feeling of blackness and ocular injection due to miosis, as well as iridocystoma, synechia of iris, cataractogenesis, retinal detachment and so on being associated with long-term consecutive application. Sympathomimetic drugs such as epinephrine and dipivefrin, with their intraocular pressure reducing activities, have also been put in clinical use, but suffer from the disadvantages such as their limited indication to open-angle glaucoma as well as accompaniment of mydriasis, blepharitis, conjunctival pigmentation, and other systemic adverse effects such as increased heart rate and elevated blood pressure. In recent years,  $\beta$ -blockers such as timolol, pindolol and carteolol, which, upon instillation to the eye, act to reduce intraocular pressure through their suppression of production of aqueous humor and offer the advantage of being free from effects on the pupil, have been used widely. However, these drugs also are defective in that they are liable to cause feeling of dryness, allergic blepharitis and superficial keratitis locally in the eye. As the only intraocular-pressure reducing agent for systemic administration, there are available carbonic anhydrase inhibitors such as acetazolamide and methazolamide, but these drugs are known to cause gastrointestinal disorders, urolithiasis and electrolyte abnormality, as well. Moreover, a report was published on the possibility that angiotensin converting enzyme inhibitors and angiotensin II antagonists, which inhibit the renin-angiotensin system governing the control of blood pressure, could be utilized as a glaucoma treatment agent, but none of these has reached the stage of commercialization for clinical application.

It was recently reported that 3-[2-(4-fluorobenzoyl)-1-piperidinyl]ethyl-2,4(1H,3H)-quinazolinedione (generic name: ketanserin), which blocks selectively serotonin (5-HT<sub>2</sub>) receptor, reduces intraocular pressure in both eyes simultaneously when applied topically to one eye (Journal of Ocular Pharmacology, vol. 3, No. 4, pp. 279 to 291, 1987).

Furthermore, JP-A-2-304022 discloses that a specifically determined type of (3-aminopropoxy)bibenzyl compound, despite of their entire difference from ketanserin in chemical structure, exhibit serotonin antagonistic activity and by virtue of this, inhibit thrombus formation and also suppress vasoconstriction, thus being particularly effective in ameliorating and improving various microcirculation disorders brought about by thrombus formation and vasoconstriction in cerebral circulatory impairments, ischemic heart diseases, peripheral circulatory disturbances and the like, but no reference is made to any intraocular-pressure reducing effect.

In developing a pharmaceutical preparation for topical ophthalmic application, special attention must be paid to ensure that such preparation will produce efficacy at the site of ocular instillation alone (to have local action) without involvement of the systemic circulatory system and central nervous system and desirably will neither affect any region other than the lesioned tissue nor exert any systemic effect. Accordingly, there is demanded the development of a pharmaceutical preparation for ophthalmologic use that possesses local action, produces lessened side-effects and permits the safe application to be realized.

In view of the above, the present inventors performed screening of various compounds in search for a 5-HT<sub>2</sub> receptor antagonist that would meet the condition of producing intraocular-pressure reducing effect at the site of administration alone and as a result, discovered that, among the (3-aminopropoxy)bibenzyl compounds described in the above-mentioned JP-A-2-304022, 2-[3-dimethylamino-2-(2-carboxyethoxy)]-propionyloxy-2'-methoxybibenzyl (generic name: sarpogrelate) or its hydrochloride (generic name: sarpogrelate hydrochloride) unexpectedly exhibits, upon instillation to the eye, improved intraocular-pressure reducing activity and is free from the shortcomings as mentioned previously.

Thus, this invention relates to:

- (1) Ophthalmic preparations for reducing intraocular pressure which comprise 2-[3-dimethylamino-2-(2-carboxyethoxy)propionyloxy]-2'-methoxybibenzyl (i.e. sarpogrelate) or a salt thereof,
- (2) Ophthalmic preparations for reducing intraocular pressure as described under the item (1), wherein the salt of sarpogrelate is 2-[3-dimethylamino-2-(2-carboxyethoxy)propionyloxy]-2'-methoxybibenzyl hydrochloride (i.e. sarpogrelate hydrochloride), and
- (3) Ophthalmic preparations for reducing intraocular pressure as described under item (1) or (2), wherein the concentration of the 2-[3-dimethylamino-2-(2-carboxyethoxy)propionyloxy]-2'-methoxybibenzyl is the range of 0.1 to 5.0 (w/v) %.

As the salt of 2-[3-dimethylamino-2-(2-carboxyethoxy)propionyloxy]-2'-methoxybibenzyl (i.e. sarpogrelate), which is usable in this invention, there are employed the pharmacologically acceptable salts, such as

salts with inorganic acids being exemplified by hydrochloride, hydrobromide, sulfate, nitrate and phosphate and salts with organic acids being exemplified by acetate, citrate, tartrate, fumarate, maleate, toluenesulfonate and methanesulfonate, with its hydrochloride (i.e. sarpogrelate hydrochloride) among others being preferable.

2-[3-Dimethylamino-2-(2-carboxyethoxy)propionyloxy]-2'-methoxybibenzyl or their salts, which are useful in the present invention, can be produced for example by the process described in JP-A-63-13427 or other processes similar thereto.

The ophthalmic preparation for reducing intraocular pressure according to the present invention can be manufactured by incorporating 2-[3-dimethylamino-2-(2-carboxyethoxy)propionyloxy]-2'-methoxybibenzyl or a salt thereof therein.

The ophthalmic preparation for reducing intraocular pressure can be provided in any pharmaceutical dosage forms that are conventionally used as an ophthalmic preparation, such as aqueous ophthalmic preparations being exemplified by aqueous ophthalmic solution, aqueous suspended ophthalmic solution, viscous ophthalmic solution and solubilized ophthalmic solution, and non-aqueous ophthalmic preparations being exemplified by non-aqueous ophthalmic solution and non-aqueous suspended ophthalmic solution.

When the ophthalmic preparation for reducing intraocular pressure according to the present invention is processed in the form of an aqueous ophthalmic solution, it is desirable to incorporate the additives which are conventionally used in aqueous ophthalmic solutions. As the additives, there are used for example preservatives, isotonicizing agents, buffers, stabilizers or pH adjusting agents.

As a preservative, there are employed parabens (e.g., methyl p-hydroxybenzoate and propyl p-hydroxybenzoate, invert soaps (e.g., benzalkonium chloride, benzethonium chloride, chlorhexidine gluconate and cetylpyridinium chloride), alcohol derivatives (e.g., chlorobutanol, phenethyl alcohol and benzyl alcohol), organic acids and their salts (e.g., sodium dehydroacetate, sorbic acid and its salts), phenols (e.g., p-chloromethoxyphenol and p-chloro-m-cresol), and organomercury compounds (e.g. thimerosal, phenylmercuric nitrate and nitromesol).

As an isotonicizing agent, for example, use is made of sodium chloride, sorbitol, mannitol and glycerol, while examples of the buffer as employed include phosphates, borates, citrates, acetates and amino acid salts, and as a stabilizer, there are used for example disodium edetate, sodium citrate, sodium polyphosphate, and sulfurous acid salts. The pH adjusting agent used includes for example hydrochloric acid, acetic acid, sodium hydroxide and phosphoric acid.

In addition, the ophthalmic preparation can also be processed by suitably formulating water-soluble high-molecular compounds or surfactants. As a water-soluble high-molecular compounds, for example, there are used cellulose derivatives, vinylic high-molecular compounds and polyhydric alcohol compounds. Examples of the cellulose derivative as used include alkylcelluloses being exemplified by methylcellulose and carboxymethylcellulose, and hydroxyalkylcelluloses being exemplified by hydroxypropylcellulose and hydroxyethylcellulose, and as a vinylic high-molecular compound, for example, use is made of polyvinylpyrrolidone, polyvinyl alcohols, polymers and ethylene-maleic anhydride copolymers, while as a polyhydric alcohol, for example, there may be used polyethylene glycol and propylene glycol. The surfactant as used includes for example non-ionic surfactants being exemplified by polysorbate and polyoxyethylene hydrogenated castor oil, cationic surfactants being exemplified by quaternary ammonium salts, and anionic surfactants being exemplified by alkyl sulfates, and amphoteric surfactants being exemplified by lecithins.

In cases where the ophthalmic preparation of the present invention is processed into the dosage form of an aqueous suspended ophthalmic solution, there are used suspending agents which are conventionally utilized in aqueous suspended ophthalmic solutions. As such suspending agent, there are used for example methylcellulose, carboxymethylcellulose, carboxyvinyl polymers, hydroxypropylmethylcellulose, polyvinyl alcohols, polyvinylpyrrolidones, macrogols (polyethylene glycols), sodium chondroitin sulfate and polysorbate 80.

The ophthalmic preparation of the present invention is advantageously used after being adjusted to a pH range which is conventionally adopted for topical application to the eye, and is normally employed after being adjusted to pH 3 to 8, preferably pH 4 to 6. For the pH adjustment, for example hydrochloric acid, acetic acid and sodium hydroxide can be used.

The ophthalmic solution of the present invention is used after being adjusted to an osmotic pressure range which is conventionally adopted for topical application to the eye, and is normally employed after being adjusted to 230 to 450 mOsm, preferably 260 to 320 mOsm. For this adjustment, for example sodium chloride, boric acid, glycerin and mannitol can be employed.

Unless contrary to the objective of this invention, the ophthalmic solution of the present invention may suitably be formulated with another medicinally active agents, in addition to 2-[3-dimethylamino-2-(2-carboxyethoxy)propionyloxy]-2'-methoxybibenzyl or a salt thereof.

The concentration of 2-[3-dimethylamino-2-(2-carboxyethoxy)propionyloxy]-2'-methoxybibenzyl or a salt thereof in the aqueous preparation for reducing intraocular pressure according to the present invention varies

depending upon for example the route of administration and symptoms of the patient, but in the case of the utilization in adult patients as an ophthalmic solution, the compound normally is processed into a preparation of a concentration in the range of 0.1 to 5.0 (w/v) %, which is preferably administered by topical application to the eye three to six times a day at a single dose of one to several drops.

Described in the following are an experiment example and examples to illustrate the present invention in more detail and to demonstrate the effects of this invention. It should be understood, however,, that these are merely illustrative and the present invention is by no means limited by them.

#### Experiment Example 1

##### Test in rabbits on the intraocular pressure reducing effect Test substance:

Used as a test substance was sarpogrelate hydrochloride dissolved in isotonic saline to a concentration of 1.0 (w/v) % and adjusted to pH 7.0. (hereinafter referred to as 1.0 % ophthalmic solution of sarpogrelate hydrochloride). Test method:

Pigmented rabbits weighing about 2 kg and having no abnormality observed in the ocular anterior chamber were subjected to measurement of intraocular pressure with use of Pneumatograph (manufactured by Alcon Co. of USA) twice 0.5 hour and immediately before topical application of the test substance, and three pigmented rabbits which showed stable intraocular pressure were utilized in the test. The abovementioned 1.0 % ophthalmic solution was applied topically in 50  $\mu$ l portions to the right eye of each of these rabbits, with isotonic saline being instilled to the left eye as a control, and measurement of intraocular pressure was taken for both eyes 0.5, 1, 2 and 4 hours after the topical application, with the intraocular-pressure measurement immediately before topical application being taken as an initial value.

##### Results:

The results are shown in Table 1 (group treated through topical application of 1.0 % ophthalmic solution of sarpogrelate hydrochloride) and Table 2 (group treated through topical application of isotonic saline). As is evident from the results shown in Tables 1 and 2, no variation in intraocular pressure was observed in the left eyes of the group treated through topical application of isotonic saline, whereas reductions in intraocular pressure were noted in the right eyes in the group treated through topical application of 1.0 % ophthalmic solution of sarpogrelate hydrochloride.

Table 1:

<u>Intraocular pressure measurements</u>					
	Intraocular pressure, mmHg				
	<u>Time after treatment, h</u>				
<u>Animal group</u>	<u>0</u>	<u>0.5</u>	<u>1</u>	<u>2</u>	<u>4</u>
Test animal A	23.0	22.0	21.5	20.5	20.0
Test animal B	23.0	22.0	21.0	21.0	20.0
Test animal C	25.0	23.0	23.0	22.0	21.0
Mean	23.7	22.3	21.8	21.2	20.3

Table 2:

Intraocular pressure measurements					
	Intraocular pressure, mmHg				
	Time after instillation, h				
Animal group	0	0.5	1	2	4
Test animal A	22.5	23.0	22.5	21.0	21.0
Test animal B	25.0	25.0	24.0	25.0	24.0
Test animal C	25.0	26.0	26.0	26.0	25.0
Mean	24.2	24.7	24.2	24.0	23.3

**Example 1 Aqueous ophthalmic solution**

An aqueous ophthalmic solution was prepared in accordance with the following formulation:

Sarpogrelate hydrochloride	1.0 g
Sodium acetate	0.05 g
Benzalkonium chloride	0.005 g
Sodium chloride	0.65 g
Sodium hydroxide	q.s.
Diluted hydrochloric acid	q.s.
Distilled water	To make the total up to 100 ml (pH 5.0)

**Example 2 Aqueous suspended ophthalmic solution**

An aqueous suspended ophthalmic solution was prepared in accordance with the following formulation:

Sarpogrelate hydrochloride	2.5 g
Concentrated glycerin	2.6 g
Disodium dihydrogenphosphate	0.5 g
Polysorbate 80	0.1 g
Benzalkonium chloride	0.005 g
Sodium hydroxide	q.s.
Diluted hydrochloric acid	q.s.
Distilled water	To make the total up to 100 ml (pH 7.0)

**Claims**

1. An ophthalmic preparation for reducing intraocular pressure which comprises 2-[3-dimethylamino-2-(2-carboxyethoxy)propionyloxy]-2'-methoxybibenzyl or a salt thereof.

2. An ophthalmic preparation as claimed in Claim 1, wherein the 2-[3-dimethylamino-2-(2-carboxyethoxy)propionyloxy]-2'-methoxybibenzyl is in the form of its hydrochloride.
3. An ophthalmic preparation as claimed in Claim 1 or Claim 2, wherein the concentration of the 2-[3-dimethylamino-2-(2-carboxyethoxy)propionyloxy]-2'-methoxybibenzyl is in the range of 0.1 to 5.0 (w/v) %.
4. The use of 2-[3-dimethylamino-2-(2-carboxyethoxy)propionyloxy]-2'-methoxybibenzyl or a salt thereof in the manufacture of an ophthalmic preparation for reducing intraocular pressure.
5. A use as claimed in Claim 4, wherein the 2-[3-dimethylamino-2-(2-carboxyethoxy)propionyloxy]-2'-methoxybibenzyl is in the form of its hydrochloride.
6. A use as claimed in Claim 4 or Claim 5, wherein the concentration of the 2-[3-dimethylamino-2-(2-carboxyethoxy)propionyloxy]-2'-methoxybibenzyl is in the range of 0.1 to 5.0 (w/v) %.



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# PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention EP 95 30 1727  
shall be considered, for the purposes of subsequent  
proceedings, as the European search report

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
T	INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE, vol. 36, no. 4, 15 March 1995 page S734 H. TAKENAKA ET AL. 'THE EFFECT OF ANPLAG (SARPOGRELATE HCL), NOVEL SELECTIVE 5-HT2 ANTAGONIST ON INTRAOCULAR PRESSURE IN GLAUCOMA PATIENTS' * the whole document *	1-6	A61K31/22 A61K31/225
T	INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE, vol. 36, no. 4, 15 March 1995 page S719 T. MANO ET AL. 'THE EFFECT OF ANPLAG (SARPOGRELATE HCL), A NEW SELECTIVE 5-HT2 ANTAGONIST ON INTRAOCULAR PRESSURE IN RABBITS' * the whole document *	1-6	
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)
			A61K
INCOMPLETE SEARCH			
<p>The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims</p> <p>Claims searched completely :</p> <p>Claims searched incompletely :</p> <p>Claims not searched :</p> <p>Reason for the limitation of the search:</p> <p>see sheet C</p>			
Place of search		Date of completion of the search	Examiner
THE HAGUE		14 September 1995	Hoff, P
CATEGORY OF CITED DOCUMENTS		<p>T : theory or principle underlying the invention</p> <p>E : earlier patent document, but published on, or after the filing date</p> <p>D : document cited in the application</p> <p>L : document cited for other reasons</p> <p>&amp; : member of the same patent family, corresponding document</p>	
<p>X : particularly relevant if taken alone</p> <p>Y : particularly relevant if combined with another document of the same category</p> <p>A : technological background</p> <p>O : non-written disclosure</p> <p>P : intermediate document</p>			

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The compound mentioned in claims 1-6 does not correspond to the formula of Sarpogrelate. However, the search has been carried out on the compound described in the examples, i.e. Sarpogrelate.





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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	DRUGS OF THE FUTURE, vol. 17, no. 12, 1992 pages 1093-1096, 'SARPOGRELATE HYDROCHLORIDE'	1-3	
Y	* the whole document * ---	3-6	
Y	JOURNAL OF PHARMACOBIO-DYNAMICS, vol. 14, no. 4, 1991 pages 177-181, K. MARUYAMA ET AL. 'MCI-9042: HIGH AFFINITY FOR SEROTONERGIC RECEPTORS AS ASSESSED BY RADIOLIGAND BINDING ASSAY' * the whole document * ---	3-6	
D,Y	JOURNAL OF OCULAR PHARMACOLOGY, vol. 3, no. 4, 1987 pages 279-290, K. KROOTILA ET AL. 'EFFECT OF SEROTONIN AND ITS ANTAGONIST (KETANSERIN) ON INTRAOCULAR PRESSURE IN THE RABBIT' * the whole document * ---	3-6	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
Y	BRITISH JOURNAL OF OPHTHALMOLOGY, vol. 77, no. 6, 1993 pages 344-348, C. COSTAGLIOLA ET AL. 'EFFECT OF TOPICAL KETANSERIN ADMINISTRATION ON INTRAOCULAR PRESSURE' * the whole document * ---	3-6	
D,X	EP-A-0 398 326 (MITSUBISHI KASEI) 22 November 1990 * abstract * * page 5, line 42 - line 46; claims; table 1 * -----	1-3	